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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,462	10/21/2003	James P. Snyder	007157/270549	4831

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,462	SNYDER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,20,23,26-30,33 and 36-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13-16,20,23,26-30,33 and 36-38* is/are allowed.

6)☐ Claim(s) *39-41,43-51 and 53-63* is/are rejected.

7)☐ Claim(s) *42 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included cancellation of claims 18, 19, 21, 22, 24, 24, 25, 31, 32, 34 and 35, addition of new claims 39-63 and amendment to claims 13, 23, 26 and 36-38, filed on 4/3/2006, is made of record. Claims 13-16, 20, 23, 26-30, 33 and 36-63 are now pending.

In view of applicants' amendment, 112 second paragraph rejection of claims 13-38 . As for 112 first paragraph rejection of claims 26-38 made in the previous office action applicants have amended the claims to limit to cancers pacifistically shown in pages 47-53 of the specification and therefore this rejection has been obviated. However, the same 112 first paragraph rejection is now applied to newly added method of use claims. As for prior art rejection of compound claims the following apply.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 2/2/2005, are made of record.

Priority

The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994).

In the instant case the provisional application dose not provide support for all subject matter embraced in the instant application. Hence, the priority to provisional application is not granted for examination of the instant application.

This passage is same as made in the previous office action. Applicants are reminded that they are not entitled for above said priority date.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60 and 62 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer and human melanoma, does not reasonably provide enablement for treating any or all cancer. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant claims 60 and 62 are drawn to "treating cancerous tissue" in general.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of VEGF/TF inhibition activity by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling

disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of VEGF/TF inhibition activity, based on limited assay, it is claimed that any or all cancers in general, which there is no enabling disclosure.
The scope of the claims includes any or all cancer due to VEGF/TF inhibition activity including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various cancers which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 42-52. The instant compounds are disclosed to have VEGF/TF inhibition activity and it is recited that the instant compounds are therefore useful in treating any or all cancer stated above for which applicants provide no competent evidence. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most cancers , are very difficult to treat and despite the fact that there are many drugs including those cited in the specification, which can be used for same VEGF/TF inhibition activity.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the any or all cancer embraced by the terms cancerous tissue.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper

proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of

the art is indicative of the requirement for undue experimentation. See Chen et al. Thromb. Haemost. 86(1): 334-345, 2001.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require VEGF/TF inhibition activity.

2) The state of the prior art: A very recent publication expressed that the VEGF/TF inhibition activity effects are unpredictable and are still exploratory. See Chen et al cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all

cancerous tissue and the state of the art is that the effects of VEGF/TF inhibition activity are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all proliferative diseases and cancers including those yet to be related to VEGF/TF inhibition activity .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action over originally presented claims 26-38 now applied to claims 60 and 62 of same scope. Limiting to the scope to specific cancers recited in currently presented claims 26 and 49 for which applicants have asserted support pointing to pages 47-53, will obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-28, 31, 34, 35 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

In view of applicants' amendment to claims13, 23, 26 to remove H and or H & alkyl (claim 26), thereby limiting the claim to only substituted alkyl besides other choices, this rejection is deemed as obviated.

However, applicants' argument is deemed as not persuasive. First of all, El-Subbagh had disclosed the above compounds in an international meeting and is entitled to 1999 date.

Secondly, applicants are not granted the priority date of the provisional application as noted above. The subject matter disclosed in the provisional application

does not include instant subject matter. Applicants are only entitled to priority date of the parent application, which is 12/2/2000.

Hence, El-Subbagh is a proper prior art.

Claims 39-41, 43 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Krapcho et al. US 3,852,279.

See example 13 on column 8.

This rejection is same as made in the previous office action dated 2/25/2005. Applicants have reintroduced the rejected compound claims again.

Claims 39-41, 43, 44, 46 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Buu-Hoi et al. Bulletin de la Societe Chimque de France, 12, 3096-3099, 1964, CA 62 : 66406, 1965. CAPLUS abstract provided.

See entire abstract for three compounds, which include N-methyl and N-benzylpiperidone compounds.

Claim 46 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Buu-Hoi et al. Compt. Rend. 251, 2725-2727, 1960, CA 55 : 112072, 1960. CAPLUS abstract provided.

See entire abstract for compounds, especially see compound 2 (RN 29053-73-4) compound 4 (RN 47084-34-4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-15, 19-20, 22-23, 25-28, 30, 32-33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

While said compounds do not anticipate the scope of instant claims in view of the amendment to exclude alkyl form R_1 definition, they are very closely related having NH in the reference versus NCH_3 in the instant claims. However, compounds that differ only in having H vs Me on nitrogen are not deemed patentably distinct absent evidence of superior or unexpected properties. See Ex parte Weston 121 USPQ 428; In re Doebel 174 USPQ 156.

Thus, one skilled in the art at the time of the invention would have been motivated to make compounds that have methyl on the nitrogen and expect the these compounds to possess the utility in the instant case in view of the close structural

similarity outlined above.

This rejection applied in the previous office action has bee deemed as obviated for reasons as noted in the above 102 rejection.

However the following apply:

Claims 39-41, 43-51 and 53-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over El-Subbagh et al. J. Med. Chem. 43: 2915-2921, 2000.

El-Subbagh et al. teaches several compounds, which include generically compounds, composition and the method of use claimed in the instant claims. See entire document especially see formula 13.

While said compound(s) doesn't anticipate the scope of instant claims, they are very closely related, being positional isomers of compounds i.e. 2-pyridyl of instant vs 4-pyridyl in the reference. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

Thus it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above. Thus, one skilled in the art at the time of the invention would have been motivated to make compounds that have 2-pyridyl based on the teaching of 4-pyridyl and expect the these compounds to

possess the utility in the instant case in view of the close structural similarity outlined above.

Allowable Subject Matter

Claims 42 and 52 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 13-16, 23, 26-30, 33 and 36-38, barring finding of any prior art in a subsequent search, are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571)

272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

6/25/2006